

WHAT IS CLAIMED IS:

1. A method of treating a disease or condition wherein inhibition of p53 activity provides a benefit comprising administering a therapeutically effective amount of a temporary p53 inhibitor to an individual suffering from the disease or condition.

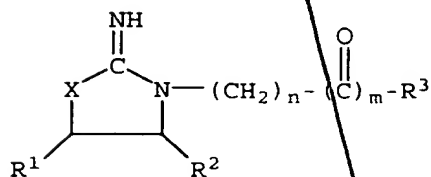
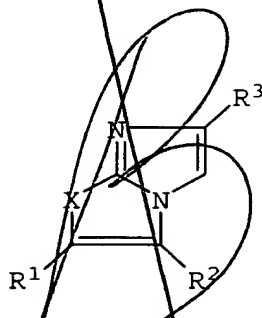
2. The method of claim 1 wherein the disease or condition comprises a p53-deficient cancerous tumor.

3. The method of claim 1 wherein the disease or condition comprises hyperthermia.

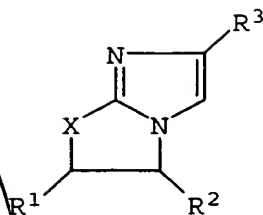
4. The method of claim 1 wherein the disease or condition comprises hypoxia, a burn, a trauma to the central nervous system, a seizure, or an acute inflammation.

5. The method of claim 1 wherein the disease or condition comprises senescence of fibroblasts.

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$$\begin{array}{c} \text{NH} \\ \parallel \\ \text{X}-\text{C}-\text{N}-(\text{CH}_2)_n-\text{C}(=\text{O})_m-\text{R}^3 \\ \diagup \quad \diagdown \\ \text{R}^1 \quad \text{R}^2 \end{array}$$


, or



and mixtures thereof,

wherein X is O, S, or NH,

m is 0 or 1,

n is 1 to 4,

R¹ and R², independently, are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkaryl, haloalkyl, haloaryl, a heterocyclic, heteroaryl, heteroaralkyl, alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, halo, (alkylthio)alkyl, (arylthio)alkyl, and (aralkylthio)alkyl,

or R¹ and R² are taken together to form an aliphatic or aromatic, 5- to 8-membered ring, either carbocyclic or heterocyclic;

R³ is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, haloaryl, heteroaralkyl, a heterocycle, alkoxy, aryloxy, halo, NR⁴R⁵, NHSO₂NR⁴R⁵, NHSO₂R⁴, and SO₂NR⁴R⁵; and

R⁴ and R⁵, independently, are selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and a heterocycle,

or R⁴ and R⁵ are taken together to form an aliphatic or aromatic, 5- to 8-membered ring, either carbocyclic or heterocyclic; and

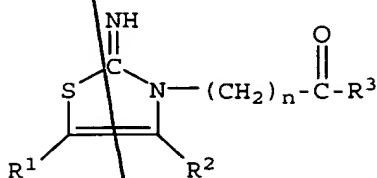
pharmaceutically acceptable salts and hydrates thereof.

7. The method of claim 6 wherein the R¹ through R⁵ groups, independently, are optionally substituted with one or more substituents selected from the group consisting of alkyl, aryl, OH, NR⁴R⁵, CN, C(=O)NR⁴R⁵, SR⁴, SO₂R⁴, CO₂R⁶, OC(=O)R⁶, OR⁶, CF₃, halo, and NO₂ wherein R⁶ is hydrogen or alkyl.

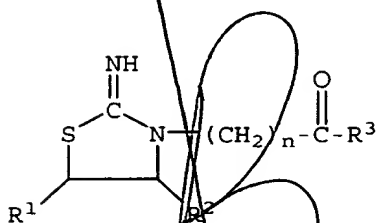
8. The method of claim 6 wherein X is S or NH; m and n each are 1; R¹ and R², independently, are selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkaryl, haloalkyl, and haloaryl, or are taken together to form a 5- or 6-membered, carbocyclic or heterocyclic ring; and R³ is selected from the group consisting of alkyl, haloalkyl, aryl, alkaryl, aralkyl, haloaryl, and a heterocycle.

9. The method of claim 6 wherein X is S; m and n each are 1; R¹ and R² are taken together to form a 5- or 6-membered aliphatic carbocyclic ring; and R³ is selected from the group consisting of alkyl, haloaryl, aryl, alkaryl, aralkyl, and a heterocycle.

10. The method of claim 6 wherein the p53 inhibitor has the structure

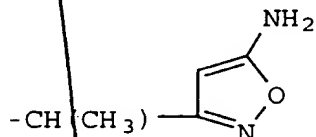


or

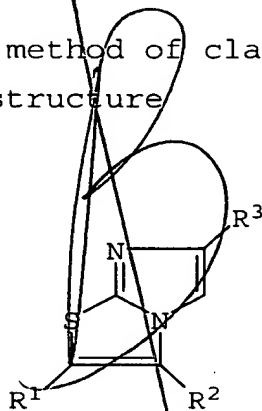


11. The method of claim 10 wherein R^1 and R^2 , independently, are selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, haloaryl, aralkyl, and alkaryl, or R^1 and R^2 are taken together to form a 5- or 6-membered ring, carbocyclic or heterocyclic; and R^3 is selected from the group consisting of alkyl, haloalkyl, aryl, alkaryl, aralkyl, and a heterocycle.

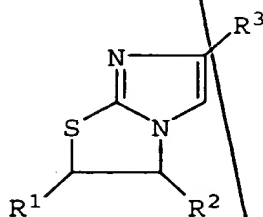
12. The method of claim 11 wherein R^3 is aryl, optionally substituted with one to three substituents selected from the group consisting of halo, CF_3 , phenyl, alkyl, nitro, and



13. The method of claim 6 wherein the p53 inhibitor has the structure

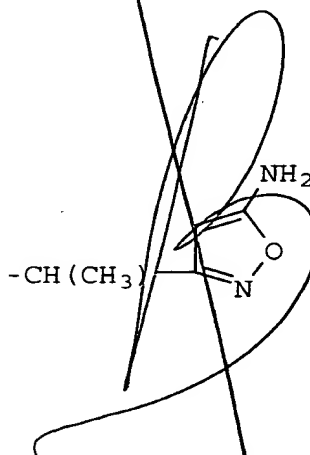


or

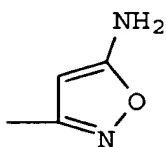


method of claim 1, are selected from the group consisting of: alkyl, aryl, alkaryl, or R¹ is a 5- or 6-membered heterocyclic; and R² is alkyl, haloalkyl, or cycloalkyl.

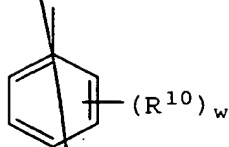
15. The method of claim 14 wherein R^1 and R^2 , independently, are selected from the group consisting of hydrogen, alkyl, haloalkyl, haloaryl, and aryl, or R^1 and R^2 are taken together to form a 5- or 6-membered carbocyclic ring; and R^3 is selected from the group consisting of aryl, haloalkyl, and alkaryl.

$$-\text{CH}(\text{CH}_3)-\text{C}(\text{N}=\text{OH})-\text{CH}_2-\text{CN}$$


, and

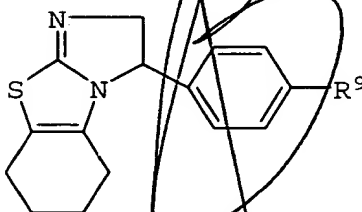


17. The method of claim 13 wherein R^3 is

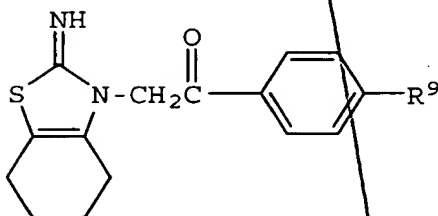


wherein w is 0 through 5, and R^{10} is selected from the group consisting of alkoxy, CF_3 , alkylthio, alkyl, aralkyl, and aryl.

18. The method of claim 6 wherein the p53 inhibitor has the structure



or

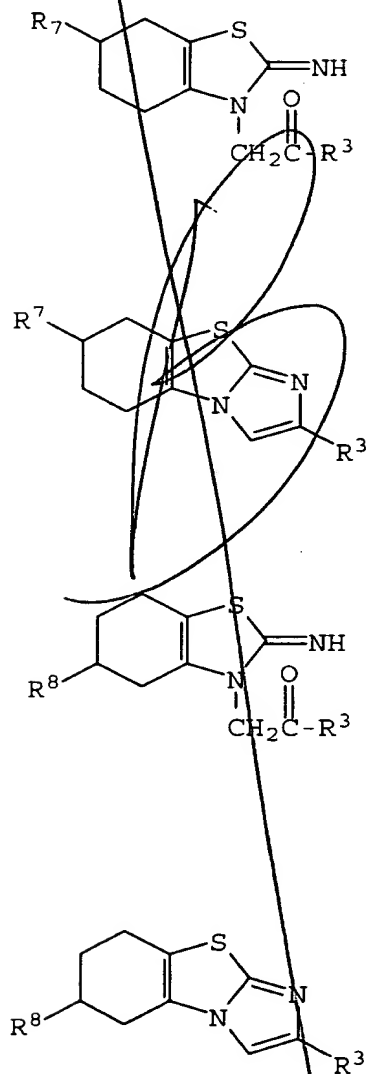


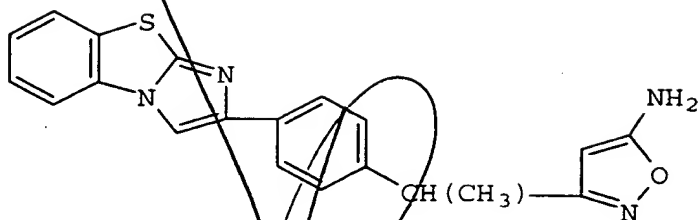
wherein R^9 is alkyl, aryl, or halo.

FIG. 10

19. The compound of claim 18 wherein R^9 is methyl, phenyl, or iodo.

20. The method of claim 6 wherein the p53 inhibitor has the structure





wherein R³ is selected from the group consisting of phenyl, 4-chlorophenyl, 4-nitrophenyl, 3-nitrophenyl, 4-methylphenyl, 4-phenylphenyl, and 4-bromophenyl; R⁶ and R⁷, independently, are hydrogen or alkyl; and R⁸ is CO₂R⁶ or hydrogen.

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22. A method of reducing or eliminating normal cell death attributable to a treatment of a disease or condition comprising administering a therapeutically effective amount of a temporary p53 inhibitor to a mammal to reversibly inhibit p53 activity.

24. The method of claim 23 wherein the disease is a cancer comprising a tumor that lacks functional p53.

26. A method of reducing or eliminating damage to normal tissue attributable to a treatment for cancer comprising administering a therapeutically effective of a temporary p53 inhibitor to a mammal to reversibly inhibit p53 activity.

28. The method of claim 26 wherein the cancer treatment comprises radiation therapy.

(a) a chemotherapeutic drug; and
(b) a temporary p53 inhibitor.

30. An improved method of treating cancer comprising administration of a therapeutically effective radiation dose to a mammal to treat a cancer, and administration of a therapeutically effective amount of a temporary p53 inhibitor to the mammal to reversibly inhibit p53 activity.

31. The method of claim 30 wherein the radiation dose and p53 inhibitor are administered simultaneously.

32. The method of claim 30 wherein the p53 inhibitor is administered prior to administration of the radiation dose.

33. A method of preventing cell death attributable to a stress-inducing event affecting the cell, said method comprising treating the cell with therapeutically effective of a compound of a temporary p53 inhibitor to reversibly inhibit p53 activity.

34. The method of claim 33 wherein the stress-inducing event comprises a cancer treatment, a trauma, hyperthermia, hypoxia, ischemia, stroke, a burn, a seizure, a tissue or organ prior to transplanting, preparing a host for bone marrow transplant, or DNA damage.

35. The method of claim 33 wherein p53 activity is inhibited for a sufficient time for the cell to recover from the stress-inducing event.

Sub B1

(a) a drug capable of treating the disease, and

37. A pharmaceutical composition comprising

(b) a carrier.

39. A method of sensitizing p53-deficient cells to a cancer therapy comprising administering, in conjunction with the cancer therapy, a sufficient amount of a temporary p53 inhibitor to a mammal to destroy p53-deficient cells that survive in an absence of the p53 inhibitor.

40. An improved method of treating cancer comprising administration of a therapeutically effective dose of a chemotherapeutic agent to a mammal to treat a cancer, and administration of a sufficient amount of a temporary p53 inhibitor to the mammal to reversibly inhibit p53 activity, wherein the dose of the chemotherapeutic agent is greater than a dose of the identical chemotherapeutic agent required to treat the cancer in the absence of administration of the p53 inhibitor.

41. The method of claim 40 wherein the mammal is free of a cancer induced by temporary p53 suppression.

42. A method of reducing or eliminating p53-mediated side effects associated with a cancer therapy comprising administering a therapeutically effective dose of a temporary p53 inhibitor to a mammal in conjunction with the cancer therapy.

43. The method of claim 42 wherein the cancer therapy comprises radiation therapy.

44. The method of claim 42 wherein the cancer therapy comprises chemotherapy.

45. The method of claim 42 wherein the p53-mediated side effect comprises one or more of hair loss, testicular cell damage, intestinal epithelia cell damage, lymphoid system damage, or hemapoietic system damage.